

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2004/004127

International filing date (day/month/year)
19.04.2004

Priority date (day/month/year)
22.04.2003

International Patent Classification (IPC) or both national classification and IPC
C12P17/18, C07D498/22, C12R1/465

Applicant
LONZA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

10/553911
International application No.
PCT/EP2004/004127

IC20 Rec'd PCT/PTO 21 OCT 2005

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:
- ☒ copy of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(a)).
 - ☐ translation of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(b)).
- Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-11
	No: Claims	
Inventive step (IS)	Yes: Claims	1-11
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-11
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

International application No.

PCT/EP2004/004127

Re Item I

Basis of the report

JC20 Rec'd PCT/PTO 21 OCT 2005

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial
applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

- D1: EP-A-0 444 503 (SQUIBB BRISTOL MYERS CO) 4 September 1991 (1991-09-04)
- D2: EP-A-0 388 962 (SQUIBB BRISTOL MYERS CO) 26 September 1990 (1990-09-26)
- D3: EP-A-0 238 011 (KYOWA HAKKO KOGYO KK) 23 September 1987 (1987-09-23)
- D4: US-A-4 524 145 (MATSON JAMES A) 18 June 1985 (1985-06-18)
- D5: EP-A-0 575 955 (KYOWA HAKKO KOGYO KK) 29 December 1993 (1993-12-29)
- D6: US-A-4 107 297 (OMURA SATOSHI ET AL) 15 August 1978 (1978-08-15)

2. Novelty and Inventive Step (Article 33(2)(3) PCT)

2.1 The present application relates to a method of recovery of staurosporine from a fermentation broth comprising steps of

- (i) adding a water-miscible organic solvent A with the fermentation broth,
- (ii) ultrafiltrating the dilute fermentation broth of step (i),
- (iii) diafiltrating the retentate of step (ii) with a mixture of water and a water-miscible organic solvent B,
- (iv) optionally adjusting the pH of the permeates to at least 8.5,
- (v) concentrating the permeates of steps (ii) and (iii) until the water-miscible organic solvents are almost removed
- (vi) adjusting the pH of the concentrate of step (v) to at least 8.5 (if necessary), and
- (vii) collecting the precipitated staurosporine.

2.2 The prior art as disclosed in documents D1 to D6 uses solvents immiscible with water in order to extract staurosporine or analogues thereof from the fermentation broths. Even if water-miscible solvents are used as extractants, a transfer into an organic phase immiscible with water is performed. A further characteristic feature of the prior art methods is the compulsory use of chromatographic methods for further purification and isolation.

None of the prior art documents describes a process for the recovery of staurosporine possessing the technical features as claimed in the present application. The subject-matter of present claims 1-11 is therefore considered novel.

2.3 Any of the cited prior art documents D1-D3, D5 or D6 can be regarded as closest prior art. All methods therein disclosed use solvents immiscible with water as extractant and chromatographic steps in order to purify or to concentrate the desired product. The problem underlying the present application can be seen as to provide an alternative method for the recovery of staurosporine. The solution is a method comprising the steps (i) to (vii) (cf point 2.1 supra). The prior art gives no motivation to the skilled person dealing with the posed problem to deviate from the mainstream teaching of the prior art, i.e. to use a two-phase-extraction/chromatography combination. The presently claimed solution is insofar not obvious in the light of the prior art. Further advantages are the avoidance of, possibly, environmentally hazardous solvents and the use of large amounts of eluents (either solutions of salts or mixtures of organic solvents with water). Both the non-obviousness of the solution and the advantages over the prior art methods justify to acknowledge the presence of inventive step for the subject-matter of present claims 1-11.

3. Industrial applicability (Article 33(4) PCT)

The subject-matter of present claims 1-11 appear to comply with the requirements of industrial applicability as stipulated in Article 33(4) PCT.

Re Item VIII

Certain observations on the international application

1. The term "almost completely removed" used in claim 1 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT.